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(54) Cytological specimen analysis system

(57) A cytological screening system assists a cytotechnologist to determine the presence of "abnormal" cells in a cytological specimen. The system includes a microscope with a motorized stage, autofocus lens, video camera and image capturing and image analysis systems.

The specimen is scanned, and cells with characteristics falling outside ranges determined by the system specifically for the specimen are marked for analysis. Analysis is performed by utilizing a set of weighted characteristics, which are based in part on the individual medical history of the patient. Cells with a combination of characteristics which fall outside a predetermined range are determined to be abnormal and are identified for further analysis by the cytotechnologist. Additionally, the system may classify a specimen as normal/abnormal, and may provide relational information and reference material for use in a manual screening process.

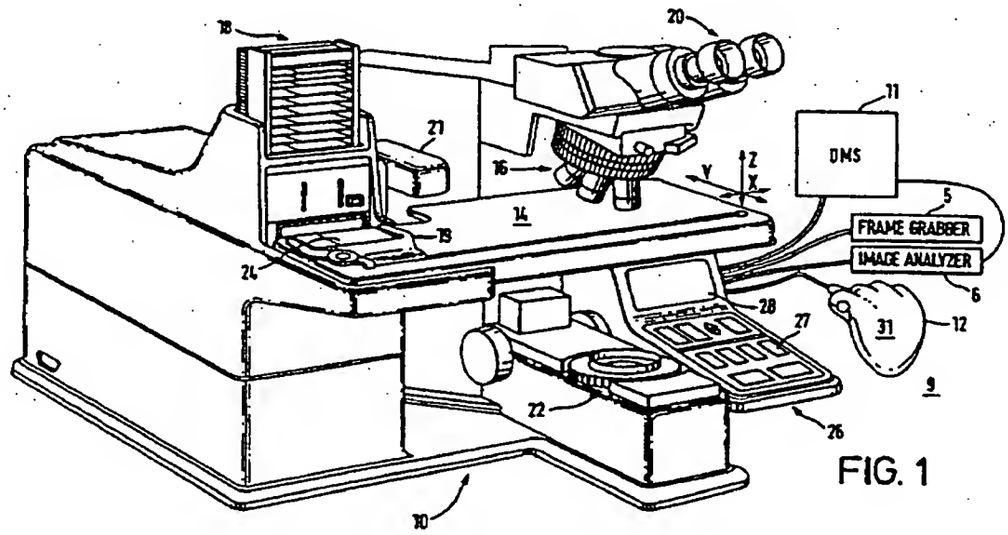


FIG. 1

GB 2 305 723 A

At least one drawing originally filed was informal and the print reproduced here is taken from a later filed formal copy.

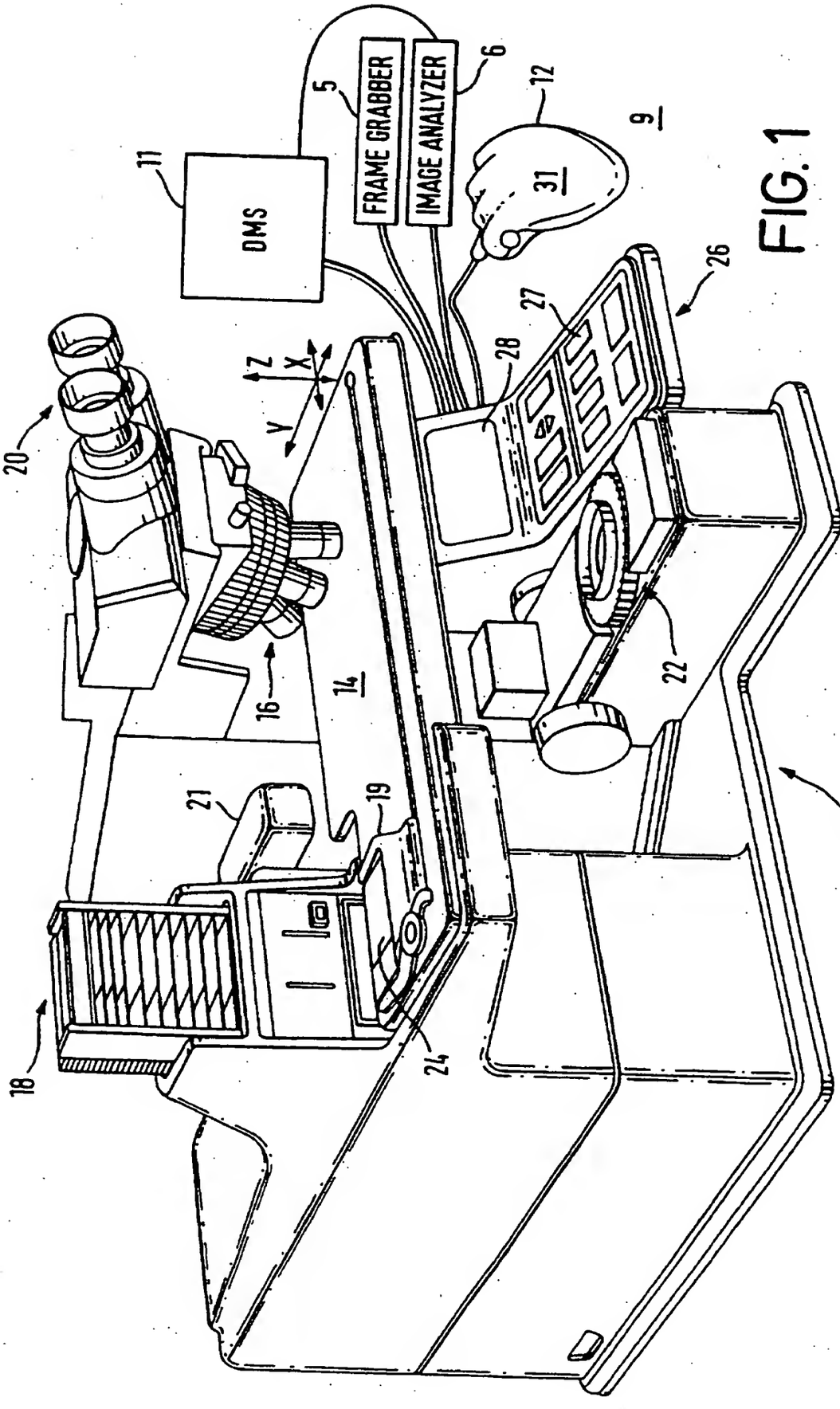
FRAME GRABBER
IMAGE ANALYZER
DMS
Z
X
Y
5
6
9
10
11
12
14
16
18
19
20
21
22
24
26
27
28
31

FIG. 1

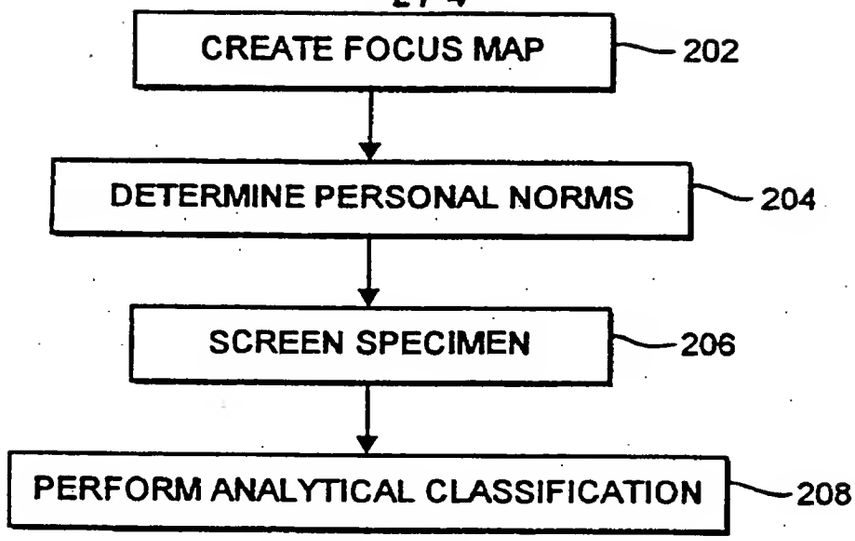
CREATE FOCUS MAP
202
DETERMINE PERSONAL NORMS
204
SCREEN SPECIMEN
206
PERFORM ANALYTICAL CLASSIFICATION
208

FIG. 2

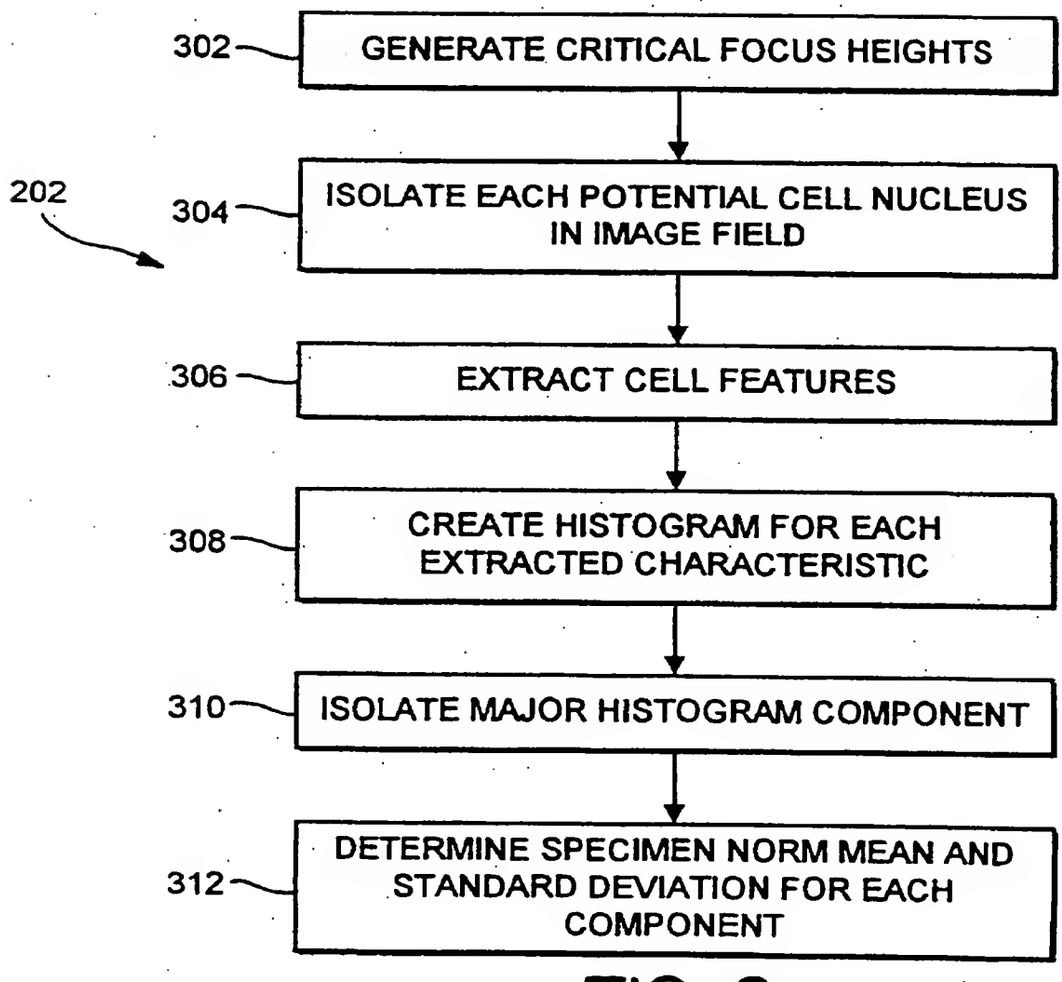
302
GENERATE CRITICAL FOCUS HEIGHTS
202
304
ISOLATE EACH POTENTIAL CELL NUCLEUS IN IMAGE FIELD
306
EXTRACT CELL FEATURES
308
CREATE HISTOGRAM FOR EACH EXTRACTED CHARACTERISTIC
310
ISOLATE MAJOR HISTOGRAM COMPONENT
312
DETERMINE SPECIMEN NORM MEAN AND STANDARD DEVIATION FOR EACH COMPONENT

FIG. 3

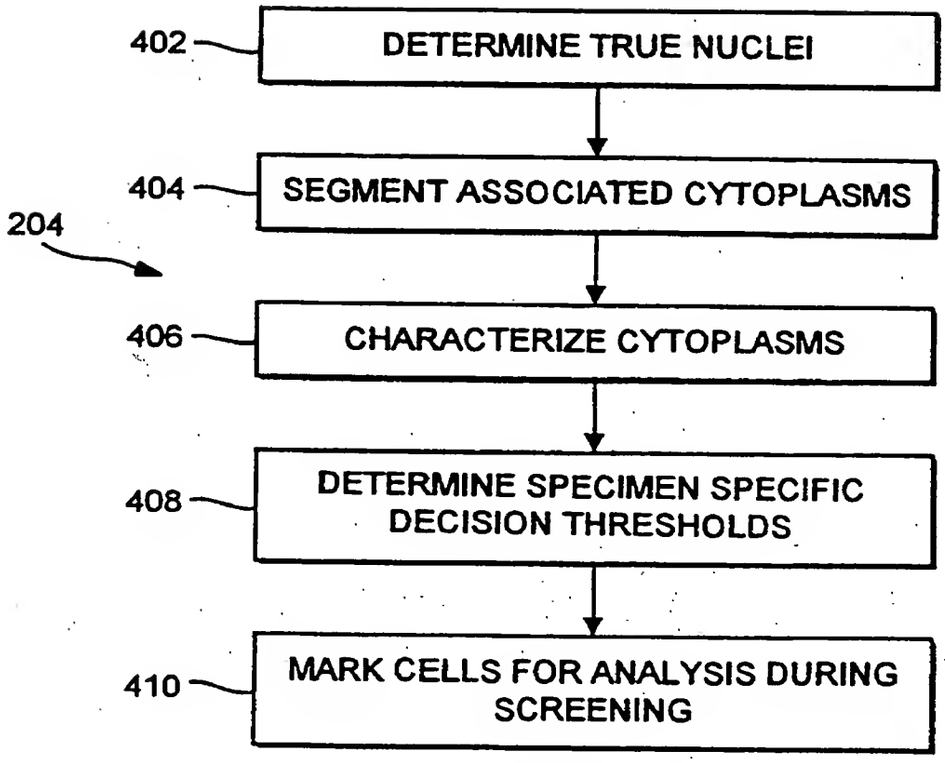
402
DETERMINE TRUE NUCLEI
404
SEGMENT ASSOCIATED CYTOPLASMS
204
406
CHARACTERIZE CYTOPLASMS
408
DETERMINE SPECIMEN SPECIFIC DECISION THRESHOLDS
410
MARK CELLS FOR ANALYSIS DURING SCREENING

FIG. 4

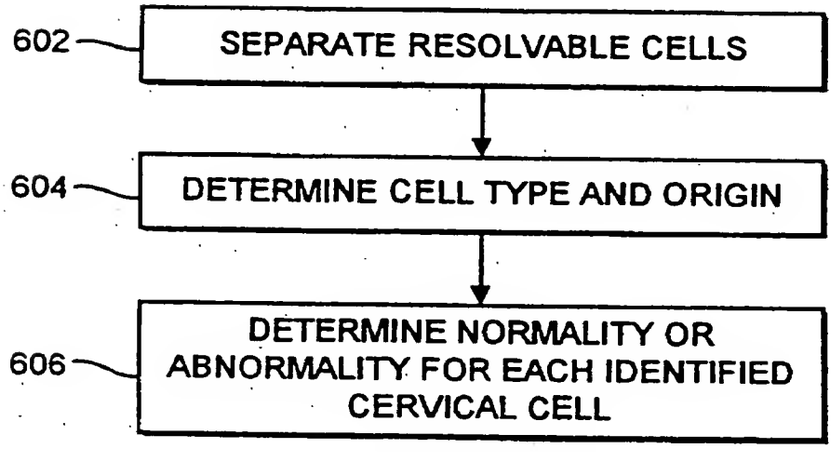
602
SEPARATE RESOLVABLE CELLS
604
DETERMINE CELL TYPE AND ORIGIN
606
DETERMINE NORMALITY OR ABNORMALITY FOR EACH IDENTIFIED CERVICAL CELL

FIG. 6

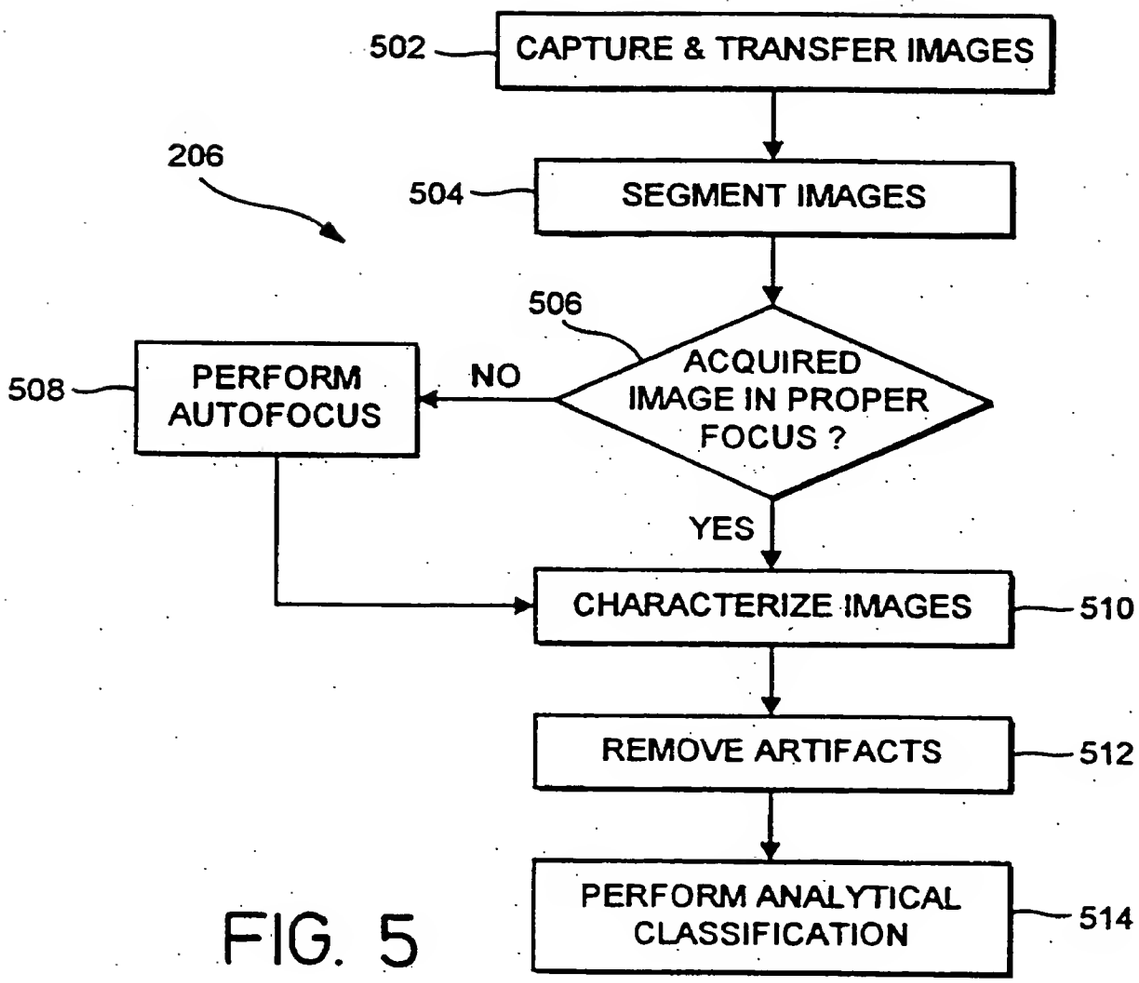
502
CAPTURE & TRANSFER IMAGES
206
504
SEGMENT IMAGES
506
ACQUIRED IMAGE IN PROPER FOCUS ?
NO
508
PERFORM AUTOFOCUS
YES
CHARACTERIZE IMAGES
510
REMOVE ARTIFACTS
512
PERFORM ANALYTICAL CLASSIFICATION
514

FIG. 5

65316.591

# CYTOLOGICAL SPECIMEN ANALYSIS SYSTEM WITH INDIVIDUALIZED PATIENT DATA

The present invention is directed generally to the field of analyzing cytological specimens to detect the presence of abnormalities in the specimen.

Proper screening of cytological specimens is an important step in the diagnosis of numerous potentially serious maladies. For instance, in the case of Pap smears which are routinely taken for women, accurate screening of the Pap smear can detect the early stages of cancer, thus reducing the chances of any cancer or related abnormal condition from spreading. Typically such screening is performed by a highly trained technician, commonly referred to as a cytotechnologist.

The interpretation of a cytological specimen is very strongly conditioned by the medical history and demographics of the particular patient. If, by way of example, a Pap smear specimen is taken early in the menstrual cycle, it will have different characteristics than one taken later in the cycle. Continuing with this example, hormonal therapies, contraceptive methods, the number of prior pregnancies and whether the patient is pre-menopausal or menopausal are a few of the other factors that can significantly influence the appearance of a specimen. The importance of medical history and demographic information to the interpretation of Pap smears is so great that the Bethesda classification system (the official system for classifying Pap specimens in the US) explicitly defines the diagnostic utility of a specimen to be "limited", that is suitable only for the diagnosis of gross abnormalities, if this information is missing or incomplete.

The cells present in a properly collected and prepared normal Pap smear represent contributions from three spatially and morphologically distinct areas of the cervical epithelium. Within each region, cells are

layered as a sequential progression of developmental stages ranging from fully mature cells on the exposed surface to very immature cells adjacent to the basal layer. An ideal normal Pap specimen consists of only mature superficial cells from the three regions of the cervical epithelium. In practice, sample technique affects the relative proportions of cells obtained from the three regions and may result in the collection of some less mature cells from underlying layers. Normal reparative changes, many of which are associated with menstrual status, may also result in the appearance of less mature cells in the specimen.

By definition, cancer is a state in which the normal controls on cell proliferation and growth are relaxed or released at an inappropriate time. Cancer related abnormalities appear in a Pap smear in a number of ways. At the grossest level, cells obtained from the superficial epithelium may have bizarre shapes. This is usually observed in well established invasive cancers. Prior to becoming invasive, cancers are often present as the appearance of a higher than expected proportion of immature cells in the specimen. The morphologies of these cells (and particularly their nuclei) usually differ visibly from those of normal cells of the same type at the same developmental stage. In the earliest stages of cancer development, subtle changes such as the non-uniform distribution of chromatin or higher than normal amount of DNA in the cell nucleus are often present and typically carry over or even become more pronounced at advanced stages.

The traditional approach taken in the development of an automated Pap smear screening instrument is to mimic some aspects of the work done by a cytotechnologist. Specifically, these systems acquire and isolate the image of a cell and interpret this image in terms of deviations from some preestablished norms based upon a "normal" specimen. One serious limitation of such systems is that from a clinical standpoint, what

is normal for any given patient is highly variable and depends upon both the medical history and demographics of that specific patent. A cytotechnologist is intensively trained to incorporate these factors into the interpretation of a specimen. Automated cytological screening instruments however, have traditionally not had access to specimen related historical and demographic information, and instead rely on population based norms. The consequence of this is that current automated screening instruments produce an excessive number of false positive results that must be reevaluated by a cytotechnologist.

Despite the importance of patient medical history and demographic data in the interpretation of Pap smears, existing automated screening instruments do not provide a means of utilizing this information. Indeed, few such systems are even directly interfaced to a system containing patient information. The few that are so interfaced can add screening results to the patient record for the purposes of report generation or can access and present this information to a cytotechnologist to aid in the manual interpretation of the automated screening results. None are designed to access patient information for automated analytical or interpretive purposes.

Viewed from a first aspect, the present invention provides a cytological specimen analysis system for use with an optical microscope for analyzing a cytological specimen obtained from a patient to identify abnormal cells in said specimen for further evaluation by a cytotechnologist comprising,

means for scanning said specimen and for marking certain cells in said specimen for classification; and

cell classifier means for classifying said marked cells as being normal or abnormal in accordance with a plurality of weighted characteristics indicative of medical characteristics of said patient.

Viewed from a second aspect, the present invention

provides a cytological specimen analysis system for use with an optical microscope for analyzing a cytological specimen obtained from a patient to determine the presence of an abnormal condition comprising:

means for creating a focus map comprising a plurality of focal points for said microscope, each of which correspond to a portion of said specimen;

means for generating a plurality of specimen norms, each of said norms corresponding to a feature of cells in said specimen;

means for scanning said specimen to capture a plurality of images of said specimen;

means, responsive to said images, for characterizing said images; and

means, responsive to said characterization, for classifying cells in said specimen in accordance with data indicative of a plurality of factors relevant to said abnormal condition to identify the presence of said abnormal condition.

Viewed from a third aspect, the present invention provides a cytological specimen analysis system for use with an optical microscope for analyzing a cytological specimen obtained from a patient to determine the presence of an abnormal condition comprising:

means, responsive to images of said specimen, for analyzing said images and marking cells in said images which exhibit a value for at least one characteristic that falls outside a range corresponding to said characteristic, said range being a function of the values of said characteristic of a plurality of cells of said specimen;

means, responsive to said marked cells, for capturing images containing said marked cells and for analytically classifying cells in said images by generating a value for each of said cells in accordance with a set of weighted characteristics indicative of predetermined medical factors of said patient and comparing said value to a predetermined value to

generate an indication of the presence of said abnormal condition.

The specimen analysis system preferably includes a motorized stage and an automatic focusing sub-system and an electronic image capturing and analyzing sub-system to allow for automatic scanning of the specimen and for electronic capture and storage of images indicative of the specimen. The use of individualized patient data advantageously reduces the number of specimens which are classified as being abnormal. Moreover, the information provided by the system enables the cytotechnologist to rapidly and accurately locate the possibly abnormal cells in the specimen.

The individualized patient data and the images of the specimen may be displayed for analysis by the cytotechnologist at various points in the process of analysis. Also, images of normal and abnormal cells may be stored in a database and displayed for the purpose of comparison to the images of the patient specimen. The patient data may be displayed after the classification of the cells as normal or abnormal. The cytotechnologist may classify cells as normal or abnormal after visual comparison of specimen images with database images.

Many cancer related cytological changes are characteristic and can be detected and classified with a high degree of accuracy by both visual and current automated methods. One major contributor of false positive results in automated systems is that many early indicators of cancer are, morphologically speaking, essentially identical to normally occurring cytological changes associated with cell repair, therapeutic treatments and/or various demographic factors. The system summarized above and described in further detail below adjusts the classification criteria on the basis of the medical history, demographics and other individual characteristics of the patient being screened to help distinguish between "normal" and "true" abnormalities in the specimen.

Population based studies of Pap smear specimens have shown that the variability of characteristics such as nuclear size among normal cells of a given type obtained from a single patient is substantially less than that determined for the same cells on a population basis. It is further recognized that variations in specimen preparation, particularly as related to the use of conventional Pap stains, can result in variations of characteristics such as integrated optical density between specimens. Each patient therefore has personal normal ranges for these characteristics in that the measured values for these characteristics can reflect both clinically significant and extraneous factors.

Basing specimen interpretation on personal/specimen specific rather than population/generic norms advantageously reduces the incidence of both false negative and false positive interpretations. The within specimen normalization of characteristics such as integrated optical density, for example, can reduce the influence of extraneous factors on interpretation and thus reduce the potential for both false positive and false negative results. Furthermore, cells lying outside of the normal range for the individual can be identified even though they lie within the normal range for the reference population. Identifying these cells reduces the possibility of a false negative. Conversely, identifying a patient whose personal norms lie toward an extreme of the population distribution can reduce the chances of a false positive determination.

Thus, the present invention, at least in its preferred embodiments, provides: a system which automatically screens cytological specimens utilizing patient information as an integral part of the screening process; a system that automates access to patient data during the manual screening of cytological specimens; and a system that provides relational information and reference material during such a manual screening process.

Some embodiments of the invention will now be described by way of example and with reference to the accompanying drawings, in which:

Figure 1 is a plan view of a preferred embodiment; and

Figures 2-6 are flowcharts showing the operation of a preferred embodiment.

Referring to Figures 1 to 6, there is shown a schematic block diagram of a system which incorporates the principles of the invention, to capture images of a specimen collected from an individual and placed upon a slide, and to analyze the specimen in accordance with data indicative of certain relevant characteristics of the individual. In Figure 1, an automated video microscope 10 with image analysis capabilities is coupled to a Data Management System (DMS) 11 which contains patient medical history and demographic data relevant to the specimens being screened. Preferably, the automated video microscope 10 is comprised of an Olympus BX-40 microscope frame, available from the Olympus Optical Corporation of Tokyo, Japan, to which a motorized stage 14, motorized focus driver (not shown) and motorized nosepiece 20 has been fitted. The microscope also includes a high resolution, scientific grade CCD video camera 7. The camera 7 is affixed to a video-port on top of the eyepieces in order to capture cell images. Preferably the video camera 7 is a Pulnix TM-1001 available from Pulnix Corp. of Sunnyvale, California. A 10X magnification, 0.4 N. A. objective lens seen at 16, provides the combination of large field of view and high spatial resolution needed for efficient specimen screening using a single objective lens.

Images received by the camera 7 are captured by a Data Raptor type frame grabber 5 available from Bit Flow Corp., Woburn, Massachusetts, and transferred to an image analyzer 6 for analysis. The microscope 10 and image analyzer 6 are coupled by a serial data link which permits the image analyzer to initiate microscope

operations to control an autofocus function on the microscope and to capture specimen position information.

The microscope 10 is preferably controlled by a controller board which is described in further detail in related patent applications entitled System for Simplifying the Implementation of Specified Functions and Multifunctional Control Unit for a Microscope.

The microscope 10 includes a moveable stage 14, a plurality of lenses 16, a slide cassette 18, slide holder 19, eyepiece 20, bar code scanner and printer 21 and light source 22. A controller board within the microscope 10 receives signals from the multifunctional control unit, controls the operation and movement of the aforesaid components of the microscope and transmits and receives information to and from DMS 11. Stage 14 is motorized and moves along an axis designated herein and seen in Figure 1 as the Y-axis. Slide holder 19 grips slide 24 and is motorized to move along an axis designated herein and seen in Figure 1 as the X-axis. Thus, movement of the stage and slide holder allows the slide to move in two-dimensions relative to the lens 16. Lens 16 is selectable, under motorized control, from a plurality of lenses. Preferably, 1 to 6 lenses are provided. Panel 26 provides a plurality of buttons 27 to allow a user of the microscope system, to enter preferences such as an initial scan rate at which the slide 24 moves underneath lens 16, the amount of overlap in the fields of view during scanning, and whether the specimen on the slide is rectangular or circular in shape. Display panel 28 provides information as to the scanning speed, information read by the bar code scanner/printer 21 and selected system status information.

The DMS 11 preferably takes the form of a programmed general purpose desktop IBM PC compatible computer which has sufficient storage and processing capability to run the Microsoft Windows operating environment and the Microsoft Visual Basic and Microsoft

Access application programs. The DMS 11 and the image analyzer 6 are preferably coupled via a high speed serial data link. The DMS 11 may also be coupled to other data processing equipment via various types of local or wide area networks.

Figure 2 of the drawings shows the four major steps executed by the system of Figure 1 to capture data from a specimen contained on a slide, and to analyze and classify the specimen to detect the presence of abnormalities. At step 202, the specimen is divided into sixty portions and a separate focus height is created for each of the portions to generate a focus map. Also at step 202, specimen norm means and standard deviations for components of the images of each of the sixty portions are generated. At step 204, thresholds, or norms, based upon the characteristics of the specimen are created for use in selecting cells for screening. At step 206, the specimen is screened by scanning the specimen, capturing images of the specimen and analytically classifying the captured images to determine the normality or abnormality of specific cells in the image. Finally, at step 208, the classification of the cells is interpreted using data specific to the patient from whom the specimen was collected.

Figure 3 of the drawings shows the steps performed at step 202 in greater detail. At step 302, the focus map is created by (a) dividing the specimen into sixty portions, (b) moving the slide so that each of the portions is beneath the lens, and (c) storing the focus height for each of the portions in the DMS. The image analysis software assists with the autofocusing of the lens. The sixty critical focus heights are used to predict the proper focus heights at intermediate points during the screening process to be described. Before moving to the next location, at step 304, a segmentation procedure is employed to isolate each potential cell nucleus in each image field. At step 306, each putative cell nucleus image is then analyzed to characterize the

nucleus by extracting a number of features including, but not limited to nuclear size and integrated optical density. In this manner, several thousand apparent cell nuclei are identified and characterized while building the focus map. Because the majority of the cells present even in a seriously abnormal specimen are normal, a histogram can be created at step 308 for each characteristic and a "normal" value extracted. A peak finding procedure is then employed to isolate the major histogram component of the putative normal cells at step 310. The resulting extracted subpopulation of cells is then analyzed statistically to determine the specimen norm mean and standard deviation for each characteristic. Some parameters such as integrated optical density can exhibit both a primary and one or more secondary maxima in their distributions. As these secondary maxima can potentially represent abnormalities such as the presence of actively dividing cells in a population of nominally mature cells, the secondary means and standard deviations are also advantageously extracted at step 312.

Figure 4 of the drawings shows the steps performed at step 204 in greater detail. Cells for which all parameters extracted from the primary peak at step 310 were within 3 standard deviations of their respective means are defined at step 402 as being true nuclei and are used as seed points in the segmentation at step 404 of the cytoplasms associated with the cells. These cytoplasms are then characterized at step 406 using procedures essentially identical to those applied to the putative cell nuclei at step 306. The result of this process is the determination of specimen norms (with standard deviations) for all primary cellular features to be used in the screening process. This information is advantageously used to compute specimen specific decision thresholds at step 408 that replace the population based decision thresholds used in the initial segmentation and feature extraction steps 304 and 306.

Cells having one or more characteristics falling outside of their respective three standard deviations limits or having characteristics corresponding to a secondary distribution maximum are marked at step 410 for analysis during the screening process. This procedure effectively customizes the segmentation and feature extraction algorithms to the characteristics of the specific specimen being screened and compensates for biological variability and differences in both specimen preparation and performance in the image acquisition chain.

Once the focus map is created at step 202 and the personal norms are computed at step 204, the screening process of step 206 is initiated. Figure 5 of the drawings shows steps performed at step 206 in greater detail. In this process, at step 502, the specimen is moved through the microscope in a step and repeat manner such that a series of overlapping images covering the entire specimen area are captured by the camera 7 and transferred through the frame grabber 5 to the image analyzer 6. Due to the massive amounts of data involved, the image from each camera frame is preferably processed separately.

The initial focus position used for each frame is as interpolated from the focus map and generally results in the acquisition of a suitably focused image. If the image is not suitably focused, then as seen at steps 506 and 508, the focal position is adjusted appropriately. The images are segmented and characterized at steps 504 and 510 as described above at steps 404 and 406 using decision thresholds computed from the previously determined personal norms.

After segmentation, but before characterization, an image contrast and gradient procedure is applied to determine whether the acquired image is in suitably sharp focus for subsequent analysis. If, as seen at step 506, adequate focus has not been achieved, at 508 an autofocus cycle is initiated and a new, better focused

image is acquired for segmentation and analysis. An artifact rejection classifier is then applied at step 512 to the extracted object characteristics to eliminate objects such as dust and bubbles from further consideration. Among the cell nucleus features used in determining the presence of artifacts are:

- nucleus size
- nucleus integrated optical density (normalized)
- nucleus perimeter size
- 1st order Hu moment for nucleus area
- 3rd order Hu moment for nucleus area
- 7th order Hu moment for nucleus area
- maximal inertia for nucleus area
- compactness of the nucleus contour
- eccentricity of the nucleus contour
- gray values skewness over the nucleus area
- gray values entropy over the nucleus area
- gray values energy over the nucleus area
- gray values contrast over the nucleus area
- gray values homogeneity over the nucleus area
- gray values correlation over the nucleus area
- combinations of the 0 - 7th Fourier descriptors
- analysis of the cytoplasm in the limited area around the nucleus.

The remaining data is applied at step 208 to a series of analytical classifiers seen in greater detail in Figure 6.

As seen in Figure 6 the analytical classifiers perform three basic functions. At a first level, free lying cells and groups of cells in which the individual cells can be resolved are separated at step 602 from cell clusters and clumps where resolution of individual cells was problematical. All of the characteristics needed for classification can be extracted for cells in the former category. Extensive cell overlap in clusters and clumps precludes the effective application of cytoplasmic classification parameters and largely necessitates classifying clusters and clumps based upon

nuclear characteristics only. However, cells within clusters and clumps are generally present in diagnostically useful morphological arrangements that are not present with free or nearly free lying cells. For this reason, free lying cells and clusters/clumps are classified separately.

The second level of classification seen at step 604 is the determination of cell type and origin based predominantly on morphological factors such as cytoplasmic shape and the location of the nucleus within the cell. One primary purpose of this classification level is to insure that specimen collection was adequate. As noted previously, proper collection of a Pap specimen requires collection of cells from three distinct regions of the cervical epithelium. If cells from all three regions cannot be identified in the specimen, classification of the specimen as being normal becomes suspect due to inadequate sampling of the critical transformation zone between the exo- and endo-cervical regions. Conversely, the presence of cells from outside of the cervical region can be an indicator of an abnormality or of improper sampling. Similarly, although Pap screening is intended for the detection of cervical cancer, many laboratories also consider the detection of bacteria, yeasts, trichomonads, fungi, bleeding, infection and similar abnormalities as important ancillary information to be obtained from this test. Properly identifying cells associated with these conditions provides both useful diagnostic information and allows a reduction in the number of cells that need to be classified for the detection of cancer related abnormalities.

The third level of classification seen at step 606 is the determination for each identified cervical cell as to whether that cell is normal or abnormal. This is traditionally accomplished using a classifier based upon population norms. The output of the classifier, whether it be based upon a statistical, fuzzy logic or neural

network methodology, is in essence a score derived from the combination of selected cell characteristics. The importance of a given characteristic to the overall score is determined by an associated weighting factor. The uniformity of chromatin distribution within a cell nucleus (nuclear texture); the presence of objects such as nuclear halos and enlarged nucleoli within the nucleus; and nuclear size are, for example, characteristics that tend to correlate strongly with the presence of abnormalities. These characteristics are given high weights in the classifier. Other characteristics are less strongly correlated and receive lower weights. In addition to characteristics extracted directly from cell images, additional characteristics may be derived and used in classification. The cell nucleus characteristics used in the classification are the same as those listed for artifact detection in step 512.

Some of these derived characteristics, such as nuclear to cytoplasmic area ratio, are "exact" in the sense that they are computed directly from primary extracted characteristics. Other derived characteristics are approximations that are useful as computationally efficient indicators. The ratio of the square of the perimeter length of an object to the area of the same object is, for example, a convenient indicator of object shape that can be used to distinguish approximately circular objects from those that are more elongated.

The process for selecting characteristics and weighting factors used in a classifier depends upon the classifier methodology used. Preferably, the difference between the classifier output and the corresponding determination made by other means such as a consensus determination by a panel of experts is minimized. A linear statistical classifier methodology based upon over sixty extracted and derived characteristics is advantageously employed. To "train" these classifiers, several thousand cells of each appropriate type on each

of over two hundred specimens were manually classified by trained cytotechnologists and cytologists. These same cells were classified automatically and the results compared using ANOVA, Simplex and Pareto analysis on both a per specimen and a population basis. After each round, the weights were adjusted until best agreement was obtained between manual and automated classification for each specimen treated individually. With these classifiers, the agreement between the results of automatic and manual classification of individual specimens was comparable to the agreement between multiple experts evaluating the same specimen. Each of the fourteen primary classifiers developed in this manner incorporate between twenty-seven and fifty characteristics.

Patient data is incorporated both explicitly and implicitly into these classifiers. Implicit incorporation results from the use of patient rather than population norms in the segmentation and extraction processes as described previously. Explicit incorporation takes the form of adjusting characteristic weights to reflect a particular aspect of patient status. For example, the weights assigned to characteristics associated with immature non-parabasal cells are increased for specimens obtained from menopausal patients to reflect the probability that the presence of these cells indicates the presence of an abnormality. The presence of parabasal cells in specimens from these same patients are, conversely given lower weight. These revised weights are assigned in the manner described above using selected subgroups of the patient database.

The limitation of the explicit approach for cell level classification is that, in the direct implementation, each possible combination of patient history and demographic variables requires the development of a new set of classifier weights based upon the evaluation of a statistically valid number of

appropriate samples in order to obtain optimal performance. This is impractical given the large number of variations possible for each of the large number of parameters involved and the difficulty of obtaining sufficient samples reflecting all of the possible combinations and permutations. A more efficient and preferable approach is to use statistical methods such as Taguchi analysis and Response Surface Modelling to permit the computation of the necessary weighting factors. This minimizes the number of unique sample populations that must be analyzed. The specific embodiment of the present invention being described screens individual Pap smear specimens and presents to the cytotechnologist for visual evaluation and classification only those cells that are not unequivocally normal.

The embodiment of the invention described above is advantageously ehhanced by the addition of an interpreter which classifies a specimen as being abnormal or normal based upon the classifications assigned to the individual cells comprising the specimen. In other words, the outputs of the multiple cell level classifiers are used as inputs to a specimen level classifier which produces an output score related to the overall degree of abnormality of the specimen. If this score exceeds a predetermined threshold, the specimen is classified as being abnormal. The statistical classifier used to interpret the cell level results is constructed as described previously. In an alternative embodiment, cells classified as being abnormal may be displayed by the DMS 11 on a computer display to allow visual inspection by the cytotechnologist. In such an embodiment the cytotechnologist may cause the display by the DMS 11 of stored images of cells that are either normal or which exhibit certain abnormal characteristics for comparison with the images obtained from the specimen. Upon visual examination of cells from the specimen, and possibly

upon comparison of the cell with stored images of cells exhibiting known characteristics, the cytotechnologist may then make a more accurate determination of the normality or abnormality of the cell. Such an embodiment advantageously allows such a determination to be made rapidly with the benefit of comparison with known cells. Moreover, if the cell is determined by the cytotcchnologist to be abnormal then the cytotechnologist may then make notations into the DMS concerning specifics of the abnormalities observed, which can then be reviewed by the patient's physician.

The foregoing steps shown in Figures 2-6 are preferably implemented in the form of a stored program which is executed by DMS 11 to implement the functions described in detail above.

A preferred embodiment of the present invention has been described herein. It is to be understood, of course, that changes and modifications may be made in the embodiment without departing from the true scope of the present invention, as defined by the appended claims.

The present application is related to the following applications which are filed concurrently herewith:

System for Simplifying the Implementation of Specified Functions
(Inventors: Richard A. Domanik, Dennis W. Gruber, and William Mayer)

Multifunctional Control Unit for a Microscope
(Inventors: Richard A. Domanik, Dennis W. Gruber, Peter G. Gombrich, William Mayer)

The present application is also related to the following U.S. applications filed on 15 September 1995:

Automated Specimen Handling System and Method for Sorting the Specimens
Filed by: Richard A. Domanik, Peter G. Gombrich, Dennis W. Gruber, and William J. Mayer

Three Dimension Mouse
Filed by: Richard A. Domanik, Peter G. Gombrich, Dennis W. Gruber, Gordon Guth, and William J. Mayer

Specimen Management System
Filed by: Richard A. Domanik, Peter G. Gombrich, and William J. Mayer

Cassette for Use with Automated Specimen Handling System
Filed by: Egon Babler, Richard A. Domanik, Peter G. Gombrich, and William J. Mayer

Each of the above applications is incorporated herein by reference.

Claims:

1. A cytological specimen analysis system for use with an optical microscope for analyzing a cytological specimen obtained from a patient to identify abnormal cells in said specimen for further evaluation by a cytotechnologist comprising,

means for scanning said specimen and for marking certain cells in said specimen for classification; and

cell classifier means for classifying said marked cells as being normal or abnormal in accordance with a plurality of weighted characteristics indicative of medical characteristics of said patient.

2. A system as claimed in claim 1 further comprising specimen classifier means responsive to classification of each of said cells for classifying said specimen as being normal or abnormal.

3. A system as claimed in claim 1 or 2 wherein said scanning means comprises:

means, responsive to said characteristics of cells of said specimen, for generating specimen specific decision threshold values indicative of acceptable initial ranges of said characteristics for cells of said specimen; and

means, responsive to said specimen specific decision threshold values, for analyzing said cells of said specimen and for marking cells having a value for at least one of said characteristics falling outside of a corresponding one of said specimen specific decision threshold values.

4. A system as claimed in any preceding claim further comprising:

cell display means for displaying selected abnormal cells in response to inputs by said cytotechnologist.

5. A system as claimed in claim 4 wherein the cell

display means further comprises means responsive to inputs by said cytotechnologist for retrieving and displaying images of cells containing known characteristics stored in said system.

INDEPENDENT CLAIM

6. A cytological specimen analysis system for use with an optical microscope for analyzing a cytological specimen obtained from a patient to determine the presence of an abnormal condition comprising:

means for creating a focus map comprising a plurality of focal points for said microscope, each of which correspond to a portion of said specimen;

means for generating a plurality of specimen norms, each of said norms corresponding to a feature of cells in said specimen;

means for scanning said specimen to capture a plurality of images of said specimen;

means, responsive to said images, for characterizing said images; and

means, responsive to said characterization, for classifying cells in said specimen in accordance with data indicative of a plurality of factors relevant to said abnormal condition to identify the presence of said abnormal condition.

INDEPENDENT CLAIM.

7. A cytological specimen analysis system for use with an optical microscope for analyzing a cytological specimen obtained from a patient to determine the presence of an abnormal condition comprising:

means, responsive to images of said specimen, for analyzing said images and marking cells in said images which exhibit a value for at least one characteristic that falls outside a range corresponding to said characteristic, said range being a function of the values of said characteristic of a plurality of cells of said specimen;

means, responsive to said marked cells, for capturing images containing said marked cells and for

analytically classifying cells in said images by generating a value for each of said cells in accordance with a set of weighted characteristics indicative of predetermined medical factors of said patient and comparing said value to a predetermined value to generate an indication of the presence of said abnormal condition.

8. A cytological specimen analysis system substantially as hereinbefore described with reference to the Figures.

The Patent Office

22

**Application No:** GB 9619296.8 **Examiner:** M. G. Clarke
**Claims searched:** 1-5, 7 and 8 **Date of search:** 21 January 1997

## Patents Act 1977
## Search Report under Section 17

**Databases searched:**

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.O): G1A AAJC

Int Cl (Ed.6): G01N 15/14, 33/ 487, 33/569

Other: ----------

**Documents considered to be relevant:**

| Category | Identity of document and relevant passage | | Relevant to claims |
|---|---|---|---|
| A | GB1439986 | Institut Elektroniki etc - whole document | |
| A | WO93/16436A1 | Neopath Inc. - whole document | |
| A | US4175860 | James W. Bacus - whole document | |

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